2022 ASCO® ANNUAL MEETING

A Phase Ia/Ib Study of CBP-1008, a Bi-specific Ligand Drug Conjugate, in Patients with Advanced Solid Tumors

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On behalf of the Leading PI, Dr. Lin Shen, and all investigators

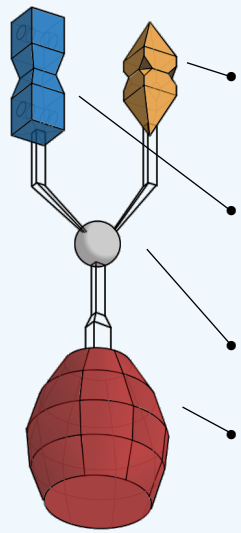
Introduction

- Folate receptor α (FRα) is a glycosylphosphatidylinositol (GPI)-anchored membrane protein. Its overexpression in tumors such as ovarian, breast and lung cancers; low and restricted distribution in normal tissues alongside emerging insights into tumor-promoting functions and association of expression with patient prognosis, together render FRα an attractive therapeutic target. [1]
- Transient Receptor Potential Cation Channel Subfamily V Member 6 (TRPV6) is clearly a valid target to disrupt further the aberrant calcium homeostasis observed in and required by many cancers. Reduction of TRPV6 activity by decreasing expression of the channel or by pharmacological intervention has shown efficacy in several cancer types: adenocarcinomas of breast, ovarian, prostate and pancreas.[2]
- CBP-1008 is a first-in-class bi-specific ligand drug conjugate, targeting FRα and TRPV6 with a high potency tubulin inhibitor payload, monomethyl auristatin E (MMAE).
- A first-in-human, multicenter, phase I study (NCT04740398) to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of CBP-1008 in solid tumors is ongoing. We herein report the preliminary result.

1. Oncotarget. 2016 Aug 9;7(32):52553-52574.
2. J Cancer. 2020 Jan 1;11(2):374-387.

About CBP-1008

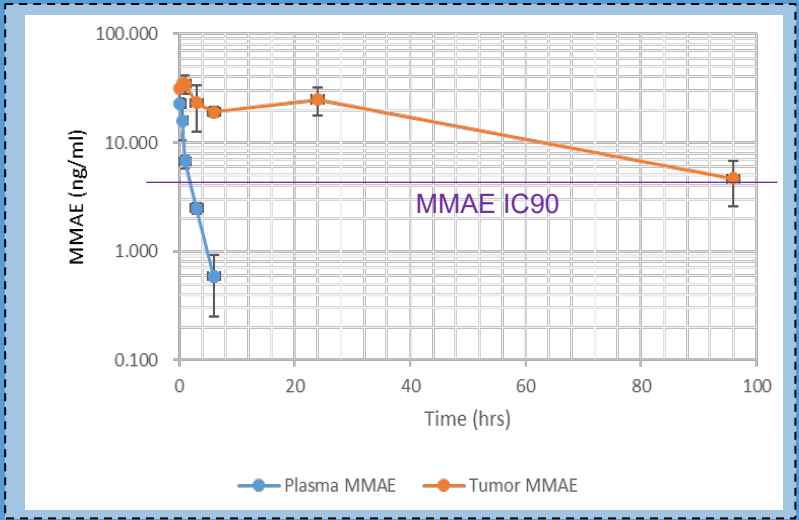
CBP-1008 is a first-in-class bi-specific ligand drug conjugate targeting FRα and TRPV6 with a high potency tubulin inhibitor payload, monomethyl auristatin E (MMAE).



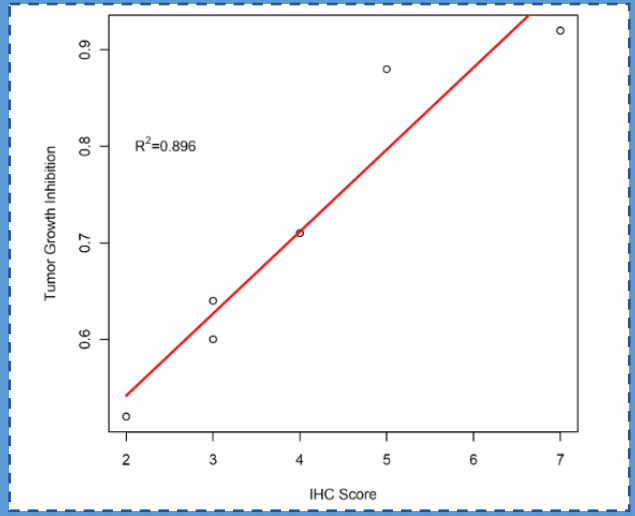
- Ligand targeting to FRα
- Ligand targeting to TRPV6
- Trifunctional linker
- Payload: MMAE

Wide Therapeutic Index

- **Fast enriched and sustained in tumor**
- **Fast systemic clearance**



Correlation between receptor expression and efficacy observed in preclinical studies

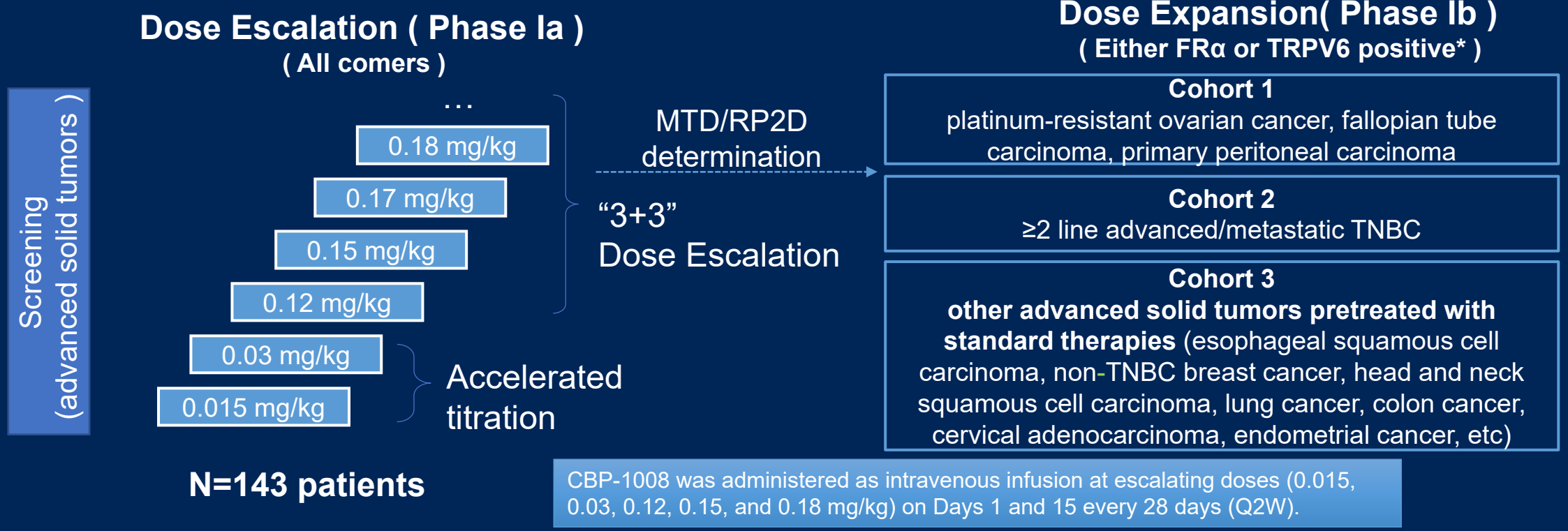


Indication selected with high expression

Target	Ovarian Cancer	TNBC	Endometrial Carcinoma	Her 2+ Breast Cancer	Lung Adeno-carcinoma
FRα	82%	39%	49%	/	55%
TRPV6	72%	74%	/	53%	35%

Study Design

- **This study is an open-label, multi-center, first-in-human phase I clinical study (NCT04740398).**



N=143 patients

CBP-1008 was administered as intravenous infusion at escalating doses (0.015, 0.03, 0.12, 0.15, and 0.18 mg/kg) on Days 1 and 15 every 28 days (Q2W).

Primary Objectives: safety, MTD.
Secondary Objectives: pharmacokinetics parameters, RP2D, and antitumor activity.

MTD: maximum tolerated dose; RP2D: recommended phase 2 dose; TNBC: triple-negative breast cancer.

*Positive criteria: ≥5% cells with moderate or strong intensity (2+, 3+)

Demographic and Baseline Characteristics

	Total N=139	Ovarian Cancer N=69
Age, median (range), years	54 (23-70)	54 (23-70)
Female, n (%)	122 (88)	69 (100)
Tumor type, n (%)		
Ovarian cancer	69 (50)	69 (100)
TNBC	25 (18)	-
Breast Cancer (non-TNBC)	16 (12)	-
Pancreatic caner	10 (7)	-
Colon cancer	6 (4)	-
Others	13 (9)	-
Prior regimens, median (range)	4 (1-11)	4 (1-11)
No. of prior regimens, n (%)		
1	8 (6)	6
2	19 (14)	5
3	30 (22)	10
4+	82 (59)	48
ECOG PS, n (%)		
0	45 (32)	26 (38)
1	94 (68)	43 (62)

ECOG: Eastern Cooperative Oncology Group

Data cut-off on 2022-02-28.

Overview of treatment-related AEs

- In phase Ia study, DLTs were observed in 3 patients (0.12, 0.15, 0.18 mg/kg, n=1 for each), including grade 4 hypophosphatemia, neutropenia, febrile neutropenia, and grade 3 hyperglycemia, alanine aminotransferase (ALT).
- MTD was not yet reached.
- CBP-1008 had a low incidence of drug-related serious adverse events, and a low incidence of dose adjustment, with no treatment-related death.

Treatment-related AEs, n (%)	Total (N=139)	
	Any grade	Grade >=3
Any treatment-related AEs	137 (99)	80 (58)
Treatment-related SAEs	11 (8)	9 (6)
Treatment-related AEs leading to dose reduction	5 (4)	4 (3)
Treatment-related AEs leading to dose interruption	31 (22)	25 (18)
Treatment-related AEs leading to discontinuation	6 (4)	6 (4)

AE: Adverse Event; SAE: Serious Adverse Event.

Treatment-related AEs in >=20% of All Patients

- **The observed TEAEs :**
  - commonly seen in anticancer therapies
  - mostly related to the cytotoxic payload
  - predictable, manageable, and preventable
- **Grade 3 or higher TEAEs :**
  - neutropenia
  - decreased white blood cell count
  - elevated AST, ALT, blood glucose, and anemia

Preferred Term, n (%)	Total (N=139)	
	Any grade	Grade >=3
Neutrophil count decreased	104 (75)	62 (44)
Pyrexia	102 (73)	0
White blood cell count decreased	96 (69)	36 (25)
Aspartate aminotransferase increased	93 (67)	7 (5)
Nausea	71 (51)	1 (1)
Alanine aminotransferase increased	69 (50)	7 (6)
Vomiting	63 (45)	2 (1)
Haemoglobin decreased	52 (37)	3 (2)
Decreased appetite	51 (37)	1 (1)
Diarrhoea	43 (31)	1 (1)
Blood glucose increased	41 (29)	1 (1)
Anaemia	39 (28)	5 (4)
Alopecia	38 (27)	0
Protein urine present	35 (25)	0
Blood triglycerides increased	29 (21)	0
Asthenia	28 (20)	2 (1)

Preliminary Antitumor Activity

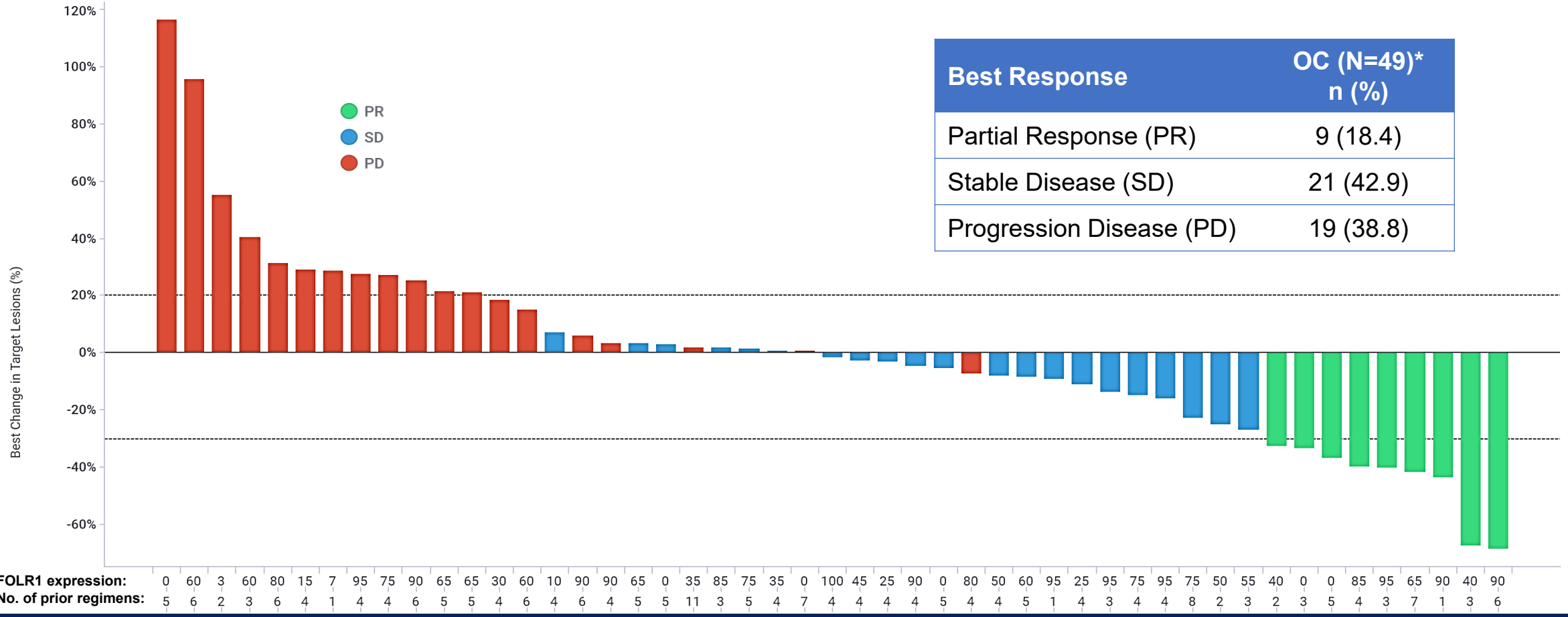
- As of 28 February 2022, 104 patients were evaluable* , 91 of whom were in CBP-1008 of ≥0.15 dose level cohorts.

	All Evaluable Patients (n=104)	Evaluable Patients in ≥0.15 dose level (n=91)
Ovarian cancer	50	49
TNBC	20	18
Breast cancer (non-TNBC)	15	15
Other	19	9

- Due to the small sample size of other tumor types, here we present the preliminary efficacy results of OC patients at dose of >= 0.15 mg/kg.

*Defined as having at least one measurable tumor at baseline and at least one evaluable post-baseline tumor response assessment

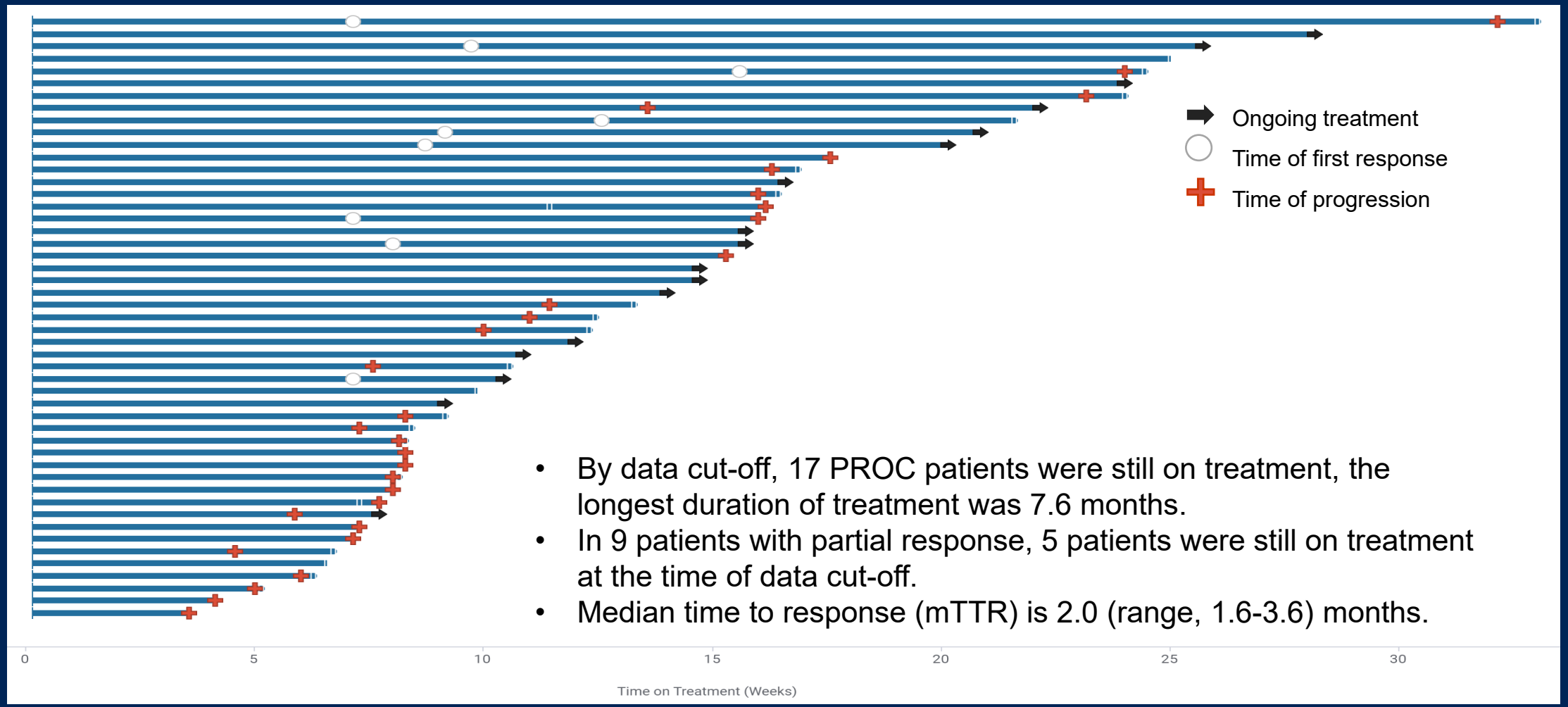
Anti-tumor Activity in All Patients with Platinum-Resistant Ovarian Cancer



Best Response	OC (N=49)* n (%)
Partial Response (PR)	9 (18.4)
Stable Disease (SD)	21 (42.9)
Progression Disease (PD)	19 (38.8)

*Patients who received >=0.15 mg/kg dose were included.

Treatment Duration and Response in All Patients with Platinum-Resistant Ovarian Cancer



- By data cut-off, 17 PROC patients were still on treatment, the longest duration of treatment was 7.6 months.
- In 9 patients with partial response, 5 patients were still on treatment at the time of data cut-off.
- Median time to response (mTTR) is 2.0 (range, 1.6-3.6) months.

Tumor Response of Platinum-Resistant Ovarian Cancer Correlates with Receptor Expression Level

- Higher response rate observed in OC patients with FOLR1/TRPV6 weighted expression score ≥85*.
- ORR significant higher for patient subpopulation with 1) >= 25% FOLR1 expression and 2) prior therapy regimens ≤ 3.

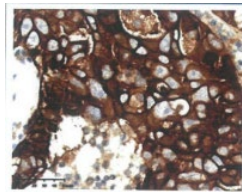
Subgroup	N*	ORR, n (%)
All patients	49	9 (**18.4**)
FOLR1 + TRPV6 expression >=85	22	6 (**27.3**)
No. of prior therapy regimens: 1-3	13	5 (**38.5**)
No. of prior therapy regimens 1-3 AND FOLR1 expression >=25	10	4 (**40.0**)

*Patients who received >= 0.15 mg/kg dose were included.

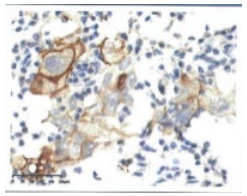
A Platinum-Resistant Ovarian Cancer Case with FOLR1 and TRPV6 Positive

Patient information： 56 years old female, diagnosed as high-grade serous carcinoma (HGSC), received 3 prior regimens before participated in this trial.

Expression		Note
FOLR1	+	weak 10%; Mid 20%; strong 70%
TRPV6	+	Weak 40%; Mid 30%; strong 15%



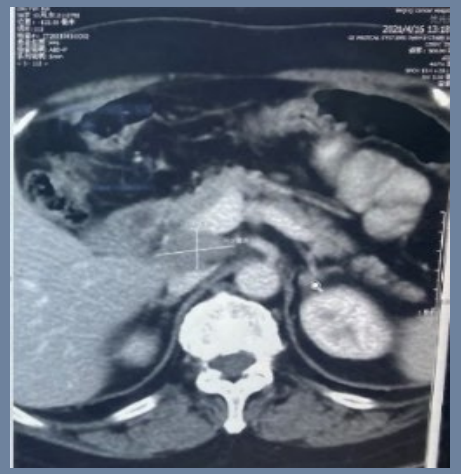
FOLR1 IHC



TRPV6 IHC

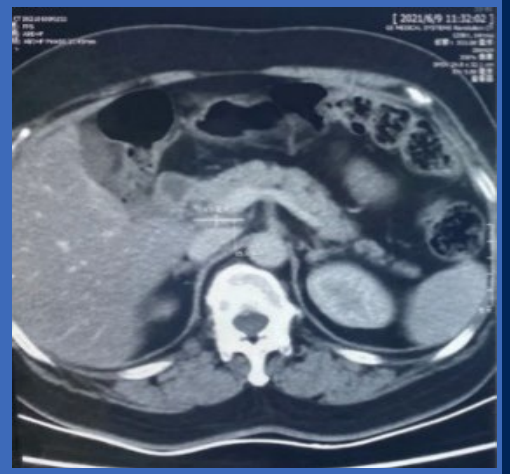
1st efficacy evaluation: target lesions were CR, overall evaluation is PR

Baseline



19.0mmx34.5mm

Visit point 1



6.3mmX25.3mm

Visit point 1=Visit point 2=Visit point 3

	Baseline	Visit point 1 (8 weeks)	Efficacy evaluation	Overall	Visit point 2 (16 weeks)
Target lesion	19 mm	6 mm	CR	**PR (-68.00%)**	**6 mm**
Non-target lesion	exist	exist	Non-PR/non-PD		
CA125	2184 U/mL	98 U/mL			40 U/mL

Summary

- The preliminary results showed that CBP-1008 has:
  - Tolerable and manageable safety profile with less dose adjustment, and no treatment-related death;
  - TEAEs mainly include neutropenia, ALT/AST increase and fever;
  - Encouraging antitumor activity at dose of >= 0.15mg/kg, especially in platinum-resistant OC patients with FRα/TRPV6 receptor expression and <= 3 regiments of prior treatment.
- A phase 2 study in patients with positive receptors expression in platinum-resistant OC is warranted.

Acknowledgements

- We thank all the patients, families, caregivers, and investigators who participated in this study.
- This study (NCT 04740398) is sponsored by Coherent Biopharma (Suzhou) Co., Ltd.